

# Experimental and Clinical Evaluation in Man of Hexamethonium (C6), A New Ganglionic Blocking Agent

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In man, C6, a new ganglionic blocking agent (50 mg. intravenously) produced inhibition of the Valsalva, tiltback and cold pressor vasopressor responses. Marked increases in digital blood flow and skin temperature with inhibition of digital reflexes to "noxious" stimuli were consistently observed (room temperature 70 F.). The increase in skin temperature was greater and more lasting than following Priscoline or tetraethylammonium chloride. Except for severe postural hypotension, side effects were minimal. Clinically the drug may be useful in the evaluation of sympathetic vasoconstriction in peripheral vascular disease as well as in the treatment of acute neurogenic vasospasm.

THE SUBSTANCES which inhibit transmission of sympathetic vasoconstrictor impulses may be divided into three main categories: (1) central blocking agents which interfere with sympathetic vasoconstrictor reflexes (cardioaortic, carotid sinus) through a central nervous system site of action, such as plasmochin<sup>1</sup> pentaquine<sup>2</sup> and the central blocking component of the DH alkaloids of ergot<sup>3</sup>; (2) adrenergic blocking agents which interrupt sympathetic nerve impulses peripherally and which also block or reverse the effects of injected epinephrine or norepinephrine, such as Dibenamine<sup>4</sup> and Priscoline<sup>5</sup>; and (3) ganglionic blocking agents of which tetraethylammonium chloride (Etamon) is the best known example. The blocking agents inhibit transmission through all autonomic ganglia including the parasympathetic as well as the sympathetic.<sup>6</sup> In addition, they enhance rather than block the pressor effects of epinephrine and norepinephrine in both man<sup>7</sup> and animals.<sup>8</sup>

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Paton and Zaimis<sup>9</sup> recently have introduced a series of polymethylene bistrimethyl ammonium salts with interesting properties; the decane derivatives (C10) exhibit curariform activity while the pentane (C5) and hexane (C6) derivatives exhibit ganglionic blocking action. The latter agents appeared to be five times as potent as tetraethylammonium salts. Studies in man by Arnold and his co-workers using C5<sup>10</sup> and by Burt and Graham using C5 and C6<sup>11</sup> suggest that these drugs produce a more complete and lasting ganglionic blockade with fewer side effects than any other agent used thus far. The purpose of the present report is to confirm and extend the observations of these British investigators on the effects of C6 in man.

## MATERIALS AND METHODS

The subjects were ward and private patients at Georgetown University Hospital, the Veterans Administration Hospital and Gallinger Municipal Hospital, Washington, D. C. Fifty-five patients were studied. Many were considered normal subjects insofar as their cardiovascular system was concerned while others were suffering from various types of peripheral vascular disease or from hypertension. The drug was given intravenously in dosages of 20 to 100 mg. of active substance dissolved in a sterile solution of either isotonic benzyl alcohol or saline. It was also given intramuscularly in doses of 40 to 60 mg.

For the hemodynamic studies of the vasopressor responses following the Valsalva maneuver, quick tiltback, and immersion of the hand in icewater, an 18 gage needle was inserted into the brachial artery through novocainized skin. This was connected to a three-way stopcock which in turn was connected to a Sanborn electromanometer. Heparin solution

was flushed through the stopcock intermittently to insure patency. All tests were carried out in a quiet room with the patient lying on a tilt-table.

Skin temperature was measured using iron-constantan wire thermocouples taped lightly to both big toes, both index fingers, umbilicus, right forearm, right upper arm and right shoulder. Two additional thermocouples were used for recording room temperature. A graphic chart of all of these ten points was automatically recorded every five minutes on a Leeds-Northrup series G "Speedomax" equipped with a multiple point recorder. This method of registration permits continuous and automatic charting of skin temperature changes without disturbance to the patient by the examiner. Room temperature varied no more than 2 degrees F. in any experiment but testing was carried out in both cool (68 to 72 F.), moderate (74 to 78 F.) and warm (78 to 86 F.) environmental temperatures in different experiments. The patient reclined semiclothed on a comfortable bed. In all instances skin temperatures reached an equilibrium and remained constant for at least 30 minutes prior to the administration of the drug. The period of observation after the drug was at least one hour.

Digital plethysmography was carried out using the Burch-Winsor plethysmograph<sup>12</sup> simultaneously with skin temperature measurements. A digital pneumatic cuff was used for venous congestion of the digits at a congesting pressure of 50 mm. Hg. Blood flow was determined according to the method of Robertson, Farmer and Smithwick.<sup>13</sup>

## RESULTS

### *Inhibition of Sympathetic Vasoconstrictor Responses*

Certain vasopressor responses, usually diminished or abolished following surgical sympathectomy, were completely blocked or definitely inhibited after 50 mg. of C6 administered intravenously. These included:

**A. Valsalva Vasopressor Overshoot.** After intravenous administration of C6, the normal vasopressor overshoot of arterial pressure following the Valsalva maneuver<sup>14</sup> was abolished in 4 out of 5 patients, and markedly inhibited in the other (fig. 1). The effect appeared in 1 to 2 minutes following injection and lasted 30 to 60 minutes or longer.

**B. Cold Pressor Response.** The cold pressor response was completely blocked in 6 and markedly inhibited in 2 of the 8 patients tested as compared with the hypertensive response before administration of C6 (fig. 2).

**C. Postural Hypotension.** All subjects developed a marked fall in arterial pressure in the

upright position, frequently to collapse levels. In addition, the usual vasopressor overshoot<sup>14</sup> which occurs on tilting back quickly from the erect to the supine position was abolished.

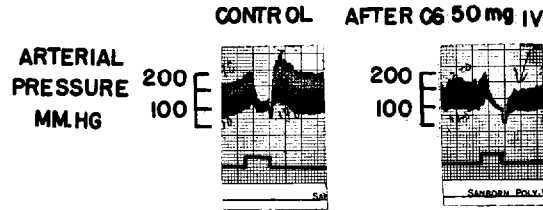


FIG. 1. Chart of arterial pressure illustrating the abolition of the vasopressor "overshoot" following Valsalva maneuver in patient E. M., a 30 year old Negro woman with essential hypertension. See text for method of recording. Paper speed was 0.5 mm. per second. The elevation of the lower line indicates the 10-second period during which the patient blew out forcibly into a closed tube. During the control period following release of the expiratory effort a momentary elevation of both systolic and diastolic pressure occurred above the basal level. After C6 this "overshoot" was abolished.

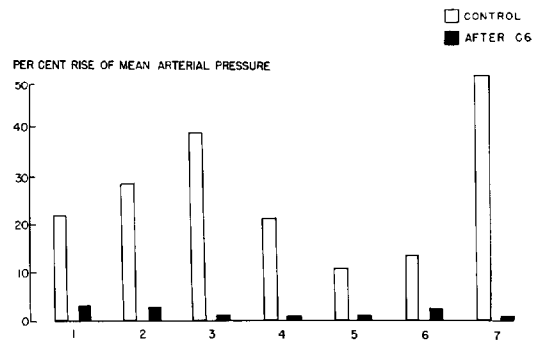


FIG. 2. Chart of the cold pressor responses before and after C6 in 7 hypertensive patients. Prior to the drug the per cent rise in mean  $\left( \frac{\text{systolic} + \text{diastolic}}{2} \right)$  arterial pressure on immersion of the hand in ice water varied between 10 and 52 per cent. Following the drug the rise in mean arterial pressure varied between 0 and 4 per cent.

**D. Congestion Collapse.** It has been demonstrated previously that after sodium nitrite or certain drugs which inhibit sympathetic vasoconstrictor reflexes collapse will occur in the supine position following venous congestion of the limbs.<sup>15</sup> This procedure was carried out by placing blood pressure cuffs proximally on both thighs and one upper arm and inflating them to pressures slightly below diastolic blood pres-

sure. Following C6 in all of 4 subjects examined a marked fall in arterial pressure with collapse occurred within three minutes after congesting the limbs, whereas prior to the drug, similar congestion of the limbs for a period of five minutes produced insignificant changes in arterial pressure in the same subjects.

#### *Arterial Pressure, Supine*

The effect of C6 on arterial pressure and pulse rate in the recumbent position was determined in 10 normotensive and 18 hypertensive patients. In the normotensive group, there was a mean fall in systolic arterial pressure of 10 per cent (range 4 to 18 per cent) and a mean fall in diastolic pressure of 7 per cent (range 0 to 20 per cent). The decrease in arterial pressure began almost immediately following injection and lasted one-half to one hour. An increase in heart rate averaging 21 beats per minute developed 1 to 2 minutes after injection and lasted 20 to 40 minutes.

In the hypertensive group the mean reduction in systolic pressure was 34 per cent with a range of 12 to 63 per cent. The average fall in diastolic pressure was 22 per cent (range 3 to 50 per cent). Thus, the reduction of both systolic and diastolic pressure was much greater in the hypertensive than in the normotensive patients. Two hypertensive patients who exhibited reductions of mean arterial pressure of 52 and 53 per cent respectively developed faintness and nausea. These symptoms and the extreme hypotension were relieved by tilting the bed into a head-down position.

#### *Skin Temperature and Digital Blood Flow*

The most marked and consistent effects of C6 were observed in the digits (fig. 3). Unlike the results obtained following dihydroergocornine<sup>16</sup> the percentage rise of digital skin temperature following C6 was greater in cool than in warm environments. Observations were made in 22 patients. Nine patients were studied in cool environments (66 to 72 F.). Following C6 in this group there was a mean rise of toe temperatures of 17 F. and an increase in finger temperatures of 11 F. Seven patients were studied in moderate environments (72 to 80 F.);

in this group the average rise in toe temperatures following C6 was 9.3 F. In warm environments (80.5 to 86.5 F.) the average increase in toe temperatures in 6 patients was 6.6 F. and

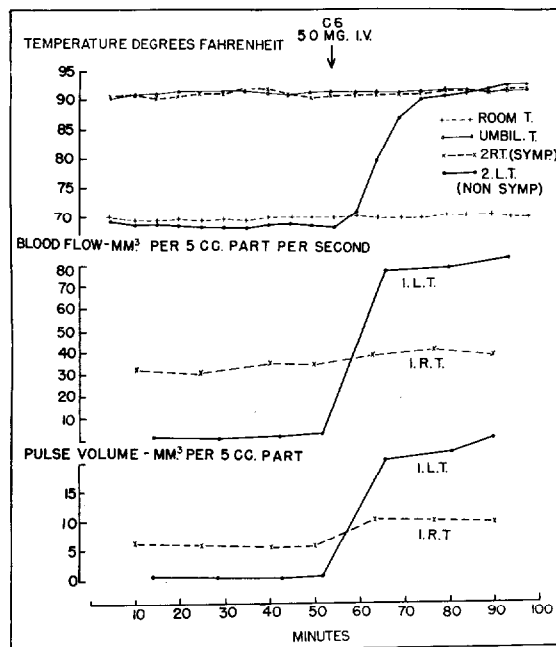


FIG. 3. Chart illustrating the effects of C6 on toe temperature, blood flow and pulse volume in patient F. A., a 28 year old woman, whose right lower extremity had been sympathectomized one year previously because of postphlebitic pain and edema. The room was maintained at a constant temperature of 70 F. throughout the experiment. In the right lower or sympathectomized extremity skin temperature recorded from the second toe was approximately 91 degrees and equalled the umbilical temperature. In the left lower (unsympathectomized) extremity the toes were cold. However, following C6 the toe temperature on the unsympathectomized side rose from 68 to 92 F. with abolition of the skin temperature gradient. The rise in blood flow and pulse volume on the unsympathectomized side paralleled the change in skin temperature. In the sympathectomized extremity there was a slight rise in blood flow and pulse volume probably indicating that the sympathectomy had not been quite complete.

in finger temperatures was 3.0 F. In all cases except those who had organic obstruction of the larger arteries the temperature gradient between the toe and umbilical temperature was abolished, this response occurring in the cool as well as in the warm room.

As noted previously by Burt and Graham<sup>11</sup> the rise in toe temperature usually was of greater degree and of longer duration than the elevation in finger temperature. Occasionally, however, the rise in finger temperature approximated the toe temperature and in 2 subjects who had an exceptionally marked vasoconstrictor response in the fingers to cold, the elevation of finger temperature exceeded that in the toes by 10 and 12 F. respectively.

The rise in digital skin temperature began in 2 to 10 minutes after intravenous injection, reached a peak in 15 to 30 minutes and then gradually subsided to pre-injection levels over a period of 2 to 6 hours. Patients often experienced a feeling of warmth in the toes and absence of sweating of the feet which sometimes persisted for as long as 6 hours.

In contrast to the poor correlation observed in subjects in warm rooms it is generally recognized that changes in digital skin temperature usually reflect changes in digital blood flow when the subject is examined in a cool room.<sup>12</sup> Nevertheless, plethysmographic measurements of digital blood flow were carried out in 6 subjects before and after the intravenous injection of 50 mg. of C6. In all cases the digital blood flow doubled and in some instances rose much higher (fig. 3). In addition, there was a marked increase in pulse volume (fig. 4) and inhibition or abolition of the vasoconstrictor response to "noxious" stimuli such as a deep breath and ice applied to the face. The increase in pulse volume and blood flow usually was greater and of longer duration in the toes than in the fingers.

#### *Comparison with TEA and Priscoline*

The marked and consistent effects of C6 on digital blood flow especially in the toes suggested that a promising clinical application of the drug might be in the field of peripheral vascular disease. It seemed advisable, therefore, to compare C6 with other agents used clinically in the diagnosis and treatment of peripheral vasospastic disorders. The response of digital skin temperature in a cool environment was used as the basis of comparison. Patients were given different drugs on consecutive days, the

room temperature being maintained at the same level each day.

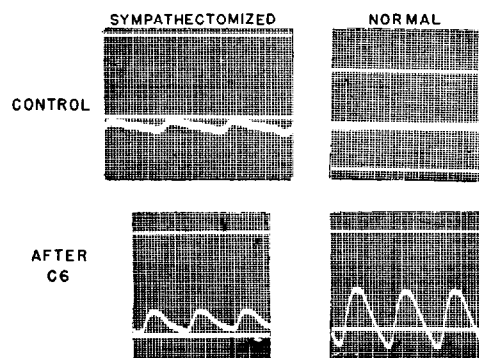


FIG. 4. Chart showing cuttings taken from the plethysmographic record of patient F. A. (fig. 3). On the sympathectomized side there was a moderate increase in pulse volume in the toe after C6. In the unsympathectomized or normal limb prior to C6 there are no perceptible pulse waves due to the marked vasoconstriction in the cool room. However, after C6 there was a marked increase in pulse volume.

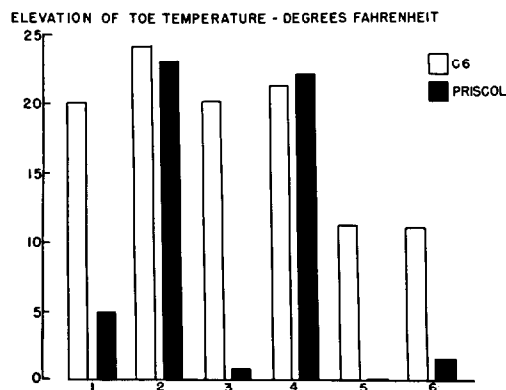


FIG. 5. Chart showing elevation of toe temperature in 6 patients given either Priscoline 50 mg. intravenously or C6, 50 mg. intravenously, on alternate days. Room temperature was maintained at the same level each day (70 degrees F. in most experiments). In cases 2 and 4 the rise in toe temperature following Priscoline equalled that following C6 but in the other 4 patients the elevation of toe temperature following C6 was significantly greater than that following Priscoline.

Six patients were given 50 mg. of Priscoline intravenously (fig. 5). Following intravenous Priscoline the duration of the rise in skin temperature was somewhat shorter than the temperature rise following C6. In all cases the in-

jection was followed by parasthesias, palpitation, flushing of the skin, nasal stuffiness and in 4 instances by shivering. The rise of digital skin temperature in this cool environment was significant in some patients and insignificant or absent in others. In cases 1 and 3 (fig. 5), the rise in toe temperature following C6 exceeded that following Priscoline by 15 and 20 F. respectively, in case 5 by 12 F. and in case 6 by 9 F. In cases 2 and 4 the rise in toe temperature after Priscoline equalled that following the injection of C6 but in these 2 cases the rise in finger temperatures was 11 and 13 degrees greater respectively following C6. In

and 18 F. respectively. In cases 1 and 3 the increase was 8 degrees greater, in case 4 it was 14 degrees and in case 5 the rise in toe temperature was 7 degrees higher following C6 than that observed after TEA. The rise in digital skin temperature following TEA was fleeting in character, lasting only 15 to 20 minutes, as compared with a duration of at least one hour following C6. Accompanying the injection of TEA all of the 6 patients studied complained of unpleasant parasthesias, a metallic taste and palpitation. These side effects were not noted after the administration of C6.

#### Site of Action

Paiton and Zaimis<sup>9</sup> demonstrated in animals that C6 produces its effects by blocking transmission through all autonomic ganglia. Positive proof of ganglionic inhibition cannot be determined readily in man. However, a similar site of action in the human is strongly suggested by the following observations: (1) the injection of small doses (12 mg.) of Priscoline intraarterially in 3 subjects resulted in a significant elevation of skin temperature in the injected limb as compared with the contralateral limb. However, intraarterial injection of 10 to 20 mg. of C6 in the same subjects resulted in no significant increase in the skin temperature of the injected limb. Thus, C6 appeared to have no peripheral vasodilating action in man. (2) True ganglionic blocking agents paralyze transmission of impulses through all autonomic ganglia including the parasympathetic as well as the sympathetic. Therefore, following C6 the parasympathetic or vagal influence on the heart should be abolished so that subsequent injection of atropine would be without effect on cardiac rate. Three patients were given 60 mg. of C6 intravenously following which the heart rate increased by 20 to 30 beats per minute. After attaining a steady state an atropinizing dose (1 mg. of atropine sulfate) was injected intravenously following which in no instance was there any further change in heart rate. (3) In contrast to drugs which inhibit transmission of sympathetic nerve impulses at other sites the ganglionic blocking agents increase the pressor effects of

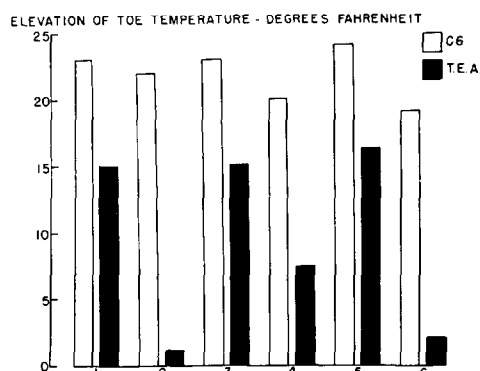


FIG. 6. Chart showing elevation of toe temperature in 6 patients given either tetraethylammonium chloride, 400 mg. intravenously, or, C6, 50 mg. intravenously, on alternate days. Experimental conditions similar to those described for figure 5. In every case the elevation of toe temperature following C6 was significantly greater than that following TEA.

another patient with far advanced arteriosclerosis obliterans of the left leg, neither C6, intravenous or intraarterial Priscoline nor lumbar paravertebral block induced with procaine resulted in any significant rise in the temperature of the toes.

Similar comparisons were made between the effects of 50 mg. of C6 given intravenously as compared to 400 mg. of tetraethylammonium given by the same route. In all of the 6 patients studied a significantly greater rise in digital skin temperature occurred following C6 as compared to TEA (fig. 6). In cases 2 and 6 (fig. 6), the rise in the toe temperature after the drug exceeded that following TEA by 20

epinephrine and norepinephrine.<sup>7</sup> In 3 normal subjects epinephrine (1  $\mu$ g. per cc.) and norepinephrine (1.5  $\mu$ g. per cc.) were given alternately by continuous intravenous infusion. Following C6 the same doses of epinephrine and norepinephrine produced significantly greater rises in arterial pressure after as compared to before the drug. These various observations strongly suggest that the site of action of C6 is at the autonomic ganglia in man as well as in animals.

#### *Dosage and Routes of Administration*

During the early phases of this investigation doses of 20 to 30 mg. were given intravenously, but at this dosage the abolition of sympathetic reflexes was inconstant. Hence, the dosage was raised to 50 mg. Intravenous doses as high as 100 mg. have been given but these seemed to be no more effective than the 50 mg. dose. The drug was also active in 50 mg. doses following intramuscular injection. However, oral and sublingual doses as high as 500 mg. were completely inactive. Thus, it would appear that for diagnostic studies or other instances in which a rapid effect is desired an intravenous dose of 50 mg. is well tolerated and effective, whereas for continuous administration the drug may be given intramuscularly in similar dosage at intervals of 3 to 4 hours.

#### *Side Effects and Tolerance*

Except for the development of severe postural hypotension the side effects following C6 were few and of minor consequence. Most patients noted no subjective sensations. Slight dilatation of the pupils frequently occurred and 12 patients complained of blurred vision which usually persisted no longer than 10 minutes. A few patients noted a dry mouth; 6 patients complained of drowsiness and 3 of transient nausea. However, there were no instances of vomiting, paresthesias, flushing, nasal stuffiness or palpitation.

The more complete the ganglionic blockade the more readily will postural collapse result. Following C6 postural hypotension persisted for as long as two hours in some patients. In a few cases tested in the supine position it was

necessary to elevate the foot of the bed slightly in order to combat a steady fall in arterial pressure. C6 has been reported to produce collapse in anesthetized individuals<sup>17</sup> and probably should never be used in patients who have suffered recent blood loss since the drug effectively blocks compensatory vasoconstrictor mechanisms.<sup>15</sup> In 2 patients with hypertension, coronary artery disease and angina pectoris a marked fall in arterial pressure in the supine position precipitated a bout of angina. Both the hypotension and the angina were relieved by elevating and passively exercising the lower extremities.

Although studies of the effect of continued treatment with C6 are still in the preliminary stages, observations in 2 patients who were given daily injections of the drug did not indicate the development of any significant degree of tolerance. For example, in a patient with thrombophlebitis 50 mg. of C6 was administered daily for eight days. On the eighth day a rise of toe temperature of 17 F. following the drug was as great as the rise following the first injection. In a similar patient 30 mg. of C6 was administered daily for four days and every other day for six days with no evidence of development of tolerance to the drug. It has not yet been determined whether tolerance develops when the drug is administered at more frequent intervals.

#### DISCUSSION

As a ganglionic blocking agent C6 differed from tetraethylammonium, the prototype of such drugs, in several important respects: (1) C6 appeared to be more potent than TEA in man since 50 mg. doses appeared to produce maximal effects. (2) The duration of action of the drug was approximately five times longer than TEA, the effects of C6 lasting 1 to 2 hours as compared with 15 to 20 minutes in the case of TEA. (3) The injection of C6 was not attended by the disturbing and unpleasant side effects of TEA such as metallic taste, generalized tingling and other paresthesias.

The most striking vasomotor effect of the drug was the marked elevation of skin temperature and blood flow in the digits, partic-

ularly in the toes. In evaluating sympathetic blocking agents it is important that the skin temperature measurements be carried out in a cool although not excessively cold environment. First, digital skin temperature and blood flow changes parallel each other only under such conditions<sup>12</sup>; and, second, sympathetic vasoconstrictor nerves to the digits are activated in cool rather than in warm environments. In fact, a hot environment may effectively abolish vasoconstrictor tone.<sup>18</sup> The importance of controlling room temperature was demonstrated in studies with dihydroergocornine,<sup>16</sup> where it was found that the drug produced a rise in digital skin temperature in warm but not in cool environments. Similarly, Priscoline will abolish the temperature gradient between the toes and the umbilicus at environmental temperatures of 77 F.<sup>5</sup> but, as shown in these studies, will not do so uniformly at room temperatures of 68 to 72 F.

As suggested by Burt and Graham<sup>11</sup> the reason that C6 usually produced a greater rise of skin temperature in the toes as compared with the fingers might be due to the greater inherent vasoconstrictor tone in the lower limbs.<sup>18</sup> This explanation is supported by the observation that in 2 patients with abnormally cold hands the rise in finger temperature exceeded that in the toes. The regular occurrence of a marked rise in toe temperature in a cool room following C6 suggests that sympathetic vasoconstrictor impulses to this area were markedly inhibited if not completely abolished. Studies are in progress to determine the extent of sympathetic block using as an index the increase in blood flow in the foot after C6 as compared with the effects of lumbar paravertebral block.<sup>19</sup>

The failure of TEA to bring about a comparable rise in skin temperature may be related more to the short duration of action of the drug rather than to its lack of potency. The skin temperature changes following C6 occurred slowly, maximum values being attained after 10 to 30 minutes. Since the duration of action of TEA is brief it is possible that the ganglionic inhibition produced by this drug was wearing off before maximum skin temperature changes could occur.

Because of the drug's potent effect on digital blood flow and skin temperature C6 may be useful in the evaluation of patients with peripheral vascular disease. In such cases the intravenous injection of C6 may provide a rapid and simple method of assessing the role of the sympathetic vasoconstrictor mechanisms without discomfort to the patient. For example, in a case of causalgia of the right hand following an old injury to the wrist C6 effectively relieved the pain and hyperesthesia for several hours. Sympathectomy was performed subsequently with complete relief of pain. In another patient with Raynaud's phenomenon characteristic color changes developed in the fingers whenever the hands were placed in cold water. This cold-induced attack was completely, although only temporarily, blocked following the injection of C6.

The drug also may be useful in the treatment of acute peripheral vascular disorders such as acute thrombophlebitis, or thrombosis or embolism of peripheral arteries whenever it is desirable to abolish the effects of reflex vasospasm. In the present study 3 cases of acute thrombophlebitis have been treated with daily injections of 50 mg. of C6. As judged by relief of pain and improvement in color and temperature of the involved foot the results seemed comparable to those usually obtained with lumbar paravertebral block induced with procaine. However, evaluation of these suggested clinical applications of C6 must await extensive studies in a large series of patients.

#### SUMMARY AND CONCLUSIONS

Hexamethonium (C6), a new ganglionic blocking agent, was administered in doses of 50 mg. intravenously to a heterogeneous group of 55 individuals including normal subjects and patients with various diseases of the vascular system with the following results:

1. Sympathetic vasopressor reflexes including the hypertensive overshoot to the Valsalva maneuver and the tiltback overshoot were inhibited or abolished. The cold pressor response was markedly inhibited, as were the reflex vasoconstrictor responses in the digits to "noxious" stimuli.

2. A significant increase in digital skin tem-

perature, usually with abolition of the temperature gradient, occurred in cool as well as in warm environments. The response was more marked in the toes than in the fingers except when the latter exhibited abnormal vasoconstriction. The rise in digital skin temperature was accompanied by simultaneous increases in digital blood flow and pulse volume as measured plethysmographically.

3. In the same subjects studies in comparable environmental temperatures (room temperature approximately 70 F. and stationary) the rise in digital skin temperature after C6 was usually greater and more prolonged than that achieved following either Priscoline (50 mg. intravenously) or tetraethylammonium (400 mg.).

4. The reduction in supine arterial pressure frequently was minimal in normotensive subjects while, although variable in degree, it was sometimes marked in hypertensive patients. Because of the inhibition of sympathetic vasoconstriction, a severe postural hypotension was a regular occurrence. For this reason the drug may precipitate vasomotor collapse in the erect or sitting position or after moderate degrees of blood loss. Occasional severe hypotensive reactions occurring in the supine position could be prevented or treated by slightly elevating the foot of the bed.

5. When injected intravenously the duration of action of the drug was 1 to 2 hours. C6 was effective by all routes of parenteral administration but was inactive after oral or sublingual administration.

6. Adverse subjective sensations such as paresthesias, palpitation, flushing, nausea, were completely absent. However, postural hypotension was severe and 2 patients with angina pectoris developed anginal attacks during severe hypotensive reactions.

Preliminary data suggest that the drug may be used clinically in the evaluation of the sympathetic vasoconstrictor component in cases of peripheral vascular disease as well as in the treatment of acute peripheral vascular disorders associated with neurogenic vasospasm.

#### ACKNOWLEDGMENT

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#### ADDENDUM

Since preparation of this paper, Turner (*Lancet* **2**: 353, 1950) has reported that doses of 1.5 to 5 Gm. of hexamethonium bromide are effective by the oral route of administration. Thus it would appear that the effective oral dose is approximately 50 to 100 times greater than the effective parenteral dose.

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